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A mathematical model for intra-cellular effects of toxins on DNA adduction and repair

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A MATHEMATICAL MODEL FOR INTRA-CELLULAR EFFECTS OF TOXINS ON DNA ADDUCTION AND REPAIR

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A MATHEMATICAL MODEL FOR INTRA-CELLULAR EFFECTS OF TOXINS ON DNA ADDUCTION AND REPAIR

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Abstract

The process by which certain classes of toxic compounds or their metabolites may react with DNA to alter the genetic information contained in subsequent generations of cells or organisms is a major component of hazard associated with exposure to chemicals in the environment. Many classes of chemicals may form DNA adducts and there may or may not be a defined mechanism to remove a particular adduct from DNA independent of replication. Many compounds and metabolites that bind DNA also readily bind existing proteins; some classes of toxins and DNA adducts have the capacity to inactivate a repair enzyme and divert the repair process competitively. This paper formulates an *intra-cellular* dynamic model for one aspect of the action of toxins that form DNA adducts, when there is a capacity for removal of those adducts by a repair enzyme combined with reaction of the toxin and/or the DNA adduct to inactivate the repair enzyme. This particular model illustrates the possible saturation of repair enzyme capacity by the toxin dosage, and shows that bistable behavior can occur, with the potential to induce abrupt shifts away from steady-state equilibria. The model suggests that bistable behavior, dose, and variation between individuals or tissues may combine under certain conditions to amplify the biological effect of dose observed as DNA adduction and its consequences as mutation. Models recognizing stochastic phenomena also indicate that variation in within-cell toxin concentration may promote jumps across stable equilibria.

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1. Introduction

This paper formulates a simple generic mathematical model for one aspect of the action of toxins that bind DNA, react to inactivate a repair enzyme, and are removed within cells. It is an *intra-cellular* dynamic model that describes a process of formation of DNA adducts when there is a capacity for removal of those adducts from the DNA by a repair enzyme. Many compounds and metabolites that bind DNA also readily bind existing proteins; some classes of toxins and DNA adducts may inactivate the repair enzyme and divert the repair process competitively (Chae et al., 1994; Lijinsky et al., 1994; Mineura et al., 1994). This particular model illustrates the possible saturation of repair enzyme capacity by the toxin dosage, and shows that bistable behavior can sometimes occur, inducing abrupt shifts between two possible steady-state equilibrium. The bistable behavior, dose, and variation between individuals or tissues may combine under certain conditions to amplify the biological effect of dose, observed as DNA adduction. Models recognizing stochastic phenomena are also discussed; stochastic variation in within-cell toxin concentration can promote jumps across stable equilibria, as shown later.

The correct replication of a cell and its DNA is essential to the differentiation and maintenance of populations of cells within tissues and ultimately within host individuals, e.g. those making up a human population. Individual diploid human cells contain approximately 6×10^9 DNA base pairs comprising about 10^6 genes Burkhart (1995). Risk assessment technology and practice benefit from insights provided by biologically-based mechanistic models. The adduct/ removal model presented here focuses only on one part of a complex intracellular process. Ultimately, models are required that describe the dynamics and behavior of dosimetry, cell surface recognition/transport, intracellular

DNA/protein interaction, repair, detoxification and clearance. At each step there is potential for a cell to control, modify, or possibly succumb to exogenously originating threats from toxic chemicals or their metabolites. Modification may also arise from interaction within cell populations through the action of exogenous signaling compounds. These interactions are to be the subjects of subsequent investigation.

2. Intra-Cellular Model of Damage and Repair

Chemical or radiological environmental stress may induce DNA damage as a *lesion*, such as a single or double DNA strand break, or oxidative- and hydroxyl radical- induced changes in structure. Damage also takes the form of an *adduct*, where reactive chemical groups may chemically react with the purine/ pyrimidine structures of DNA to disrupt hydrogen bond pairing or the action of polymerases (B. Singer, 1985; for review see *Drinking Water and Health.*). The adducted DNA, if not repaired by removal of the alkyl or aryl group may result in an altered DNA sequence (mutation) that is passed on to subsequent daughter cells. Depending on the site (gene) that is mutated, many biological outcomes are conceivable. If the event contributes to abnormal cell cycle regulation, such that the cell becomes a candidate for entry into the carcinogenic process, the interaction is of particular interest.

The most frequently described adducts have been methylated or ethylated nucleotides generated by direct alkylating agents (Bronstein et al., 1992; Pegg et al., 1990) These provide examples of the importance of the process in terms of mutation and the potential for biological variation between tissues and individuals to have profound effects on the mutagenic/carcinogenic outcome (Fox and Margison, 1988; Bronstein et al., 1991). Many toxic compounds are also likely to bind intra-cellular proteins, such as those involved in the removal of an

adduct from the DNA. There also may be a "suicide" reaction wherein the repair enzyme becomes inactivated and is thus removed from the population of molecules available for subsequent use by the cell in DNA repair (Hora et al., 1983; Pegg and Byers, 1992).

DNA adduction is one case among several possibilities, but it serves to motivate formulation of the generic mathematical models to follow. These are simplified extensively, but do capture some of the essentials of an adduct formation-repair/removal process in the presence of a toxic chemical and repair enzyme. Examination of the results of the model then suggests questions concerning system dynamics that are relevant to other intra- and extra-cellular processes, and to risk assessment. These must ultimately be answered by appropriate experiments.

2.1 Deterministic Mathematical Model

Suppose the cell in question is viewed at time t, where t may be measured from cell birth. To be specific let it be a stem cell, possibly in the spleen, cf. Alberts *et al.* (1994), so during time t the cell may have produced a number of daughter cells, while itself remaining alive.

We initially write a deterministic kinetic model to represent the system, utilize the following notation: $A(t)$ is the (mean) number of adducts present on the DNA of the cell, $R(t)$ is the (mean) number or concentration of *repair enzyme*, e.g. alkyl DNA transferase, present in the cell interior, and $T(t)$ is the concentration of the toxic chemical, or metabolite thereof, simultaneously present in the cell, all at time t. These quantities are stipulated to satisfy the following differential equations:

$$\frac{dA(t)}{dt} = \underbrace{\lambda_0 + \lambda_1 T(t)}_{\text{Adduct formation}} - \underbrace{\mu_{RA} R(t) A(t)}_{\substack{\text{Adduct removal/repair} \\ \text{by enzyme} \\ \text{(DNA transferase)}}} - \underbrace{\delta_{AM} A(t)}_{\substack{\text{Adduct removal} \\ \text{by mutation (plus} \\ \text{spontaneous disappearance)}}} \tag{2.1}$$

$$\frac{dT(t)}{dt} = \underbrace{\tau_C(t)}_{\substack{\text{Toxin input} \\ \text{to cell interior}}} - \underbrace{\delta_T T(t)}_{\substack{\text{Toxin removal;} \\ \text{other agents}}} - \underbrace{\mu_{RT} R(t) T(t)}_{\substack{\text{Toxin removal;} \\ \text{binds with} \\ \text{"suicide repair enzyme"} \\ \text{(DNA transferase)}}} \tag{2.2}$$

$$\frac{dR(t)}{dt} = \underbrace{\beta\left(\overline{R} - R(t)\right)}_{\text{Enzyme creation}} - \underbrace{\delta_R R(t)}_{\substack{\text{Enzyme removal;} \\ \text{life-in-cell effect}}} - \underbrace{\mu_{RA} R(t) A(t)}_{\substack{\text{Enzyme removal} \\ \text{by adduct repair}}} - \underbrace{\mu_{RT} R(t) T(t)}_{\substack{\text{Enzyme removal;} \\ \text{binds with toxin}}} \tag{2.3}$$

These equations exhibit the possible double amplification effect of a toxin on adduct formation: first, the toxin contributes to the rate of adduct formation in accordance with rate parameter λ_1, (see (2.1)); secondly, it is in competition for the repair enzyme, thus depleting the enzyme's level, in accordance with the rate parameter μ_{RT} (see (2.2)). The expression $\delta_T T(t)$ in 2.2 includes loss of toxin as a result first, of its removal during adduct formation as in (2.1); second, because of normal cellular processes such as detoxification or binding to DNA and proteins. Both a cell DNA adduct-enzyme product and a toxin-enzyme product may be induced; one example among many is the binding of benzylguanine to the alkyl DNA transferase (Chae et al., 1994).

The reader needs no reminder that the above model makes many simplifying assumptions, all of which may be questioned and modified as empirical information is developed. For example, the self-limiting enzyme creation term $\beta\left(\overline{R} - R(t)\right)$ may be wrong in detail; even if adequate in mathematical form the upper limit, $\overline{R}$, may depend upon individual variation, tissue, cell age or cumulative exposure to toxin, possibly history-dependent expressed as an integral functional of $T(t')$, $0 \le t' \le t$. Similar comments may be made concerning

all of the rate parameters, λ_0 through μ_{RT}. For the present all parameters will be treated as constants. One aim of our modeling is to expose unexpected effects and sensitivities, and some such are revealed even for the present simplified setup. All assumptions made are hypothetical artifacts of the model until verified empirically, but may serve to suggest particular experiments.

3. Steady-State Solution

Suppose all parameters and the toxin input, τ_C, are *temporarily* assumed to be constants. If there is a long-run steady-state solution for $(A(t), T(t), R(t))$ then it satisfies the non-linear algebraic equations obtained by putting the derivatives equal to zero. In the present case steady-state solutions are obtained by solving the derivative = zero (2.1) for A in terms of R, (2.2) for T in terms of R, and finally putting these into (2.3). The result is

$$\beta\overline{R} = (\beta + \delta_R)R + \mu_{RA}\left(\frac{\lambda_0}{\delta_{AM} + \mu_{RA}R} + \frac{\lambda_1\tau_C}{(\delta_T + \mu_{RT}R)(\delta_{AM} + \mu_{RA}R)}\right)R + \frac{\mu_{RT}\tau_C R}{\delta_T + \mu_{RT}R}; \tag{3.1}$$

after multiplying out by the denominator there results a cubic equation for the fixed points which are the appropriate solutions of (3.1). Although parametric solutions can be found for (3.1) it will not be easy to extract general qualitative information from them; see Appendix. A straightforward alternative is to introduce hypothetical biologically plausible parameters and to solve the differential equations (2.1), (2.2), and (2.3) numerically; this has been done in some trial cases.

Alternatively, qualitative information can be obtained from the formula (3.1), written as follows:

$$\beta(\bar{R}-R)=\delta_R R+\left(\frac{\lambda_0\mu_{RA}}{\delta_{AM}+\mu_{RA}R}+\frac{\tau_C\mu_{RT}}{\delta_T+\mu_{RT}R}\right)R \qquad (3.1a)$$
$$+\frac{\lambda_1\tau_C\mu_{RA}R}{(\delta_T+\mu_{RT}R)(\delta_{AM}+\mu_{RA}R)}$$

or

$$\ell(R)=r(R)\equiv r_1(R)+r_2(R)+r_3(R).$$

Graph the left-hand side of the above as a function of R, written $\ell(R)=\beta(\bar{R}-R)$ vs. the right-hand side, $r(R)=r_1(R)+r_2(R)+r_3(R)$ where $r_1(R)=\delta_R R$, $r_2(R)=\left(\frac{\lambda_0\mu_{RA}}{\delta_{AM}+\mu_{RA}R}+\frac{\tau_C\mu_{RT}}{\delta_T+\mu_{RT}R}\right)R$, $r_3(R)=\left(\frac{\lambda_1\tau_C\mu_{RA}R}{(\delta_T+\mu_{RT}R)(\delta_{AM}+\mu_{RA}R)}\right)$.

Points of crossing are candidate solutions. Note the following possible qualitative configuration of the above components:

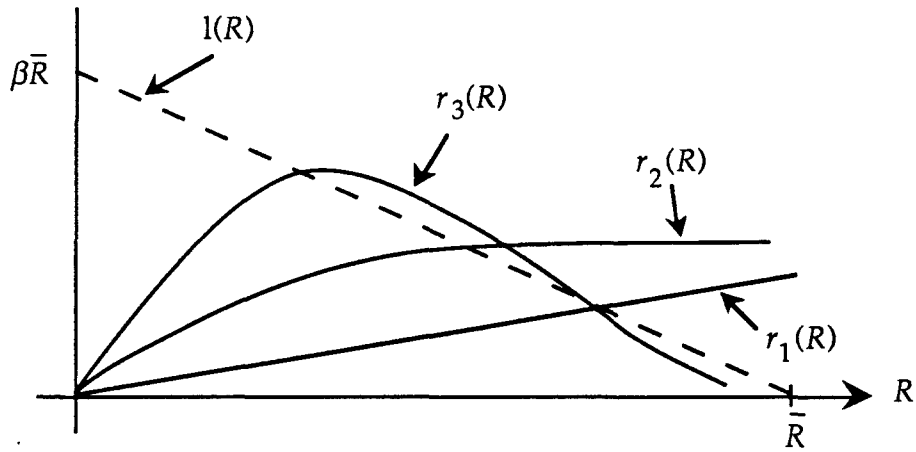

Figure 1

Now if the r.h.s. components are summed the following qualitative possibilities may emerge:

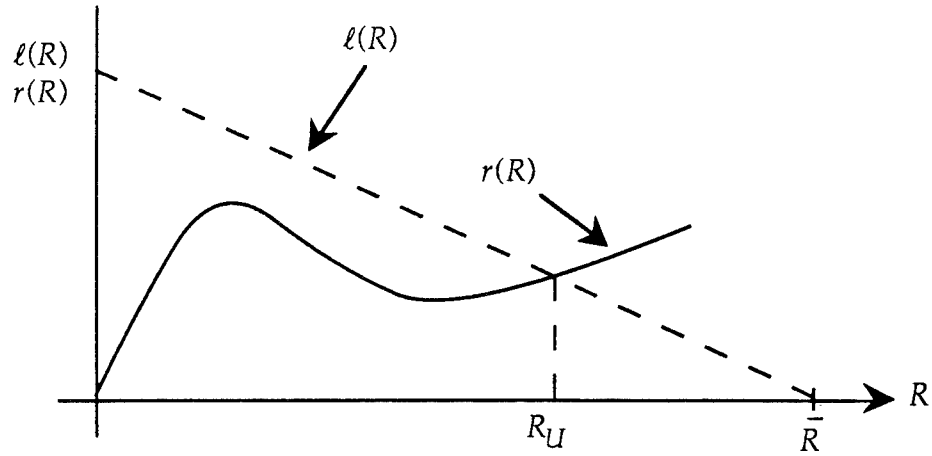

Figure 2A

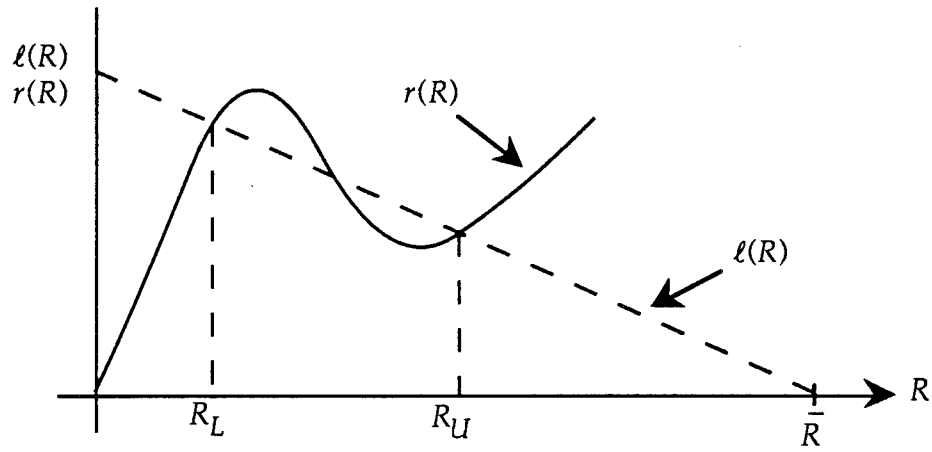

Figure 2B

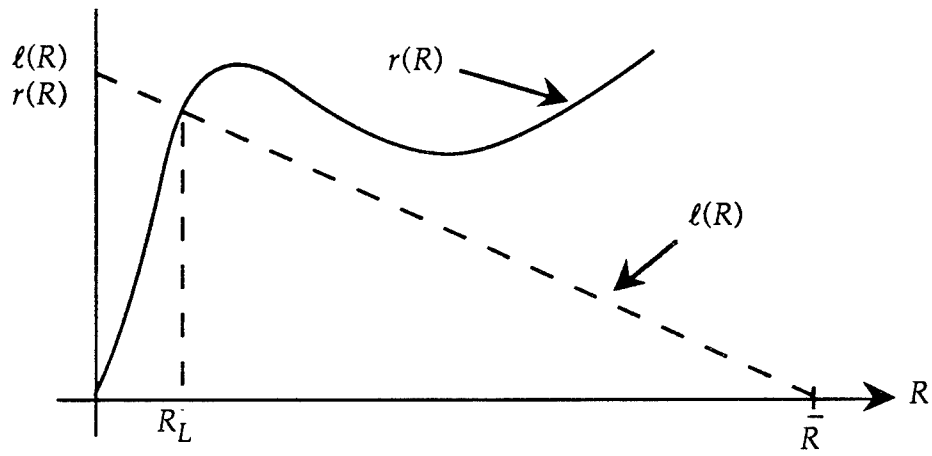

Figure 2C

The curve crossings, at values R_U and R_L in Figure 2, actually represent local equilibrium points; cf. Beltrami (1987). It is conjectured (and has been verified numerically in trial cases by examination of eigenvalues for the linearized system, using MATLAB) that in case the oscillating behavior of $r(R)$ occurs as shown, the value R_U in Fig. 2A, R_U and R_L in Fig. 2B, and R_L in Fig. 2C are all local stable points near which $R(t)$ will tend to reside as t increases, provided the starting level is near one of these values. If toxin dosage to the cell, τ_C, is low this is consistent with a relatively high level of enzyme, see formulas $r_2(R)$ and $r_3(R)$ in (3.1a) and Fig. 2A. If τ_C is high this is consistent with relatively low ambient enzyme: Fig. 2C. The intermediate equilibrium point in Fig. 2B is presumably always locally unstable. Fig. 2B suggests the existence of *two* such stable points, R_U and R_L; if the enzyme level starts near one of these it tends to reside nearby, but if a disturbance (the origin of which is not modeled here) occurs, the enzyme level may abruptly shift, e.g. from R_U to R_L, consistent with a high level of ambient toxin *and* a relatively high formation rate for adducts. Switches back and forth could even occur. Such behavior has been called *bistable*. The conditions described tend to be associated with a relatively high rate of fixation by mutation when $R(t)$ is near R_L, with subsequent damaging effects. However, other protective behavior, such as apoptosis (programmed cell death), may be stimulated to inhibit overall adduct fixation and tumor production. Apoptosis is not modeled here.

3.1 Stochastic Model (Simulation)

The above deterministic model can be "made stochastic" in several ways, but the simplest, if not most elegant and complete, is to *computer-simulate*: (a) discretize time in equal-sized steps, (b) allow a discrete-time version of (2.1) to define the mean of a Markov stochastic process with (c) Normal/Gaussian

increments whose mean(s) are defined as in (b), and with variance equal to (or proportional to) the above incremental means, as would be appropriate for a diffusion approximation of a simple birth-death process. Formalize as follows, making time steps unity on an appropriate scale.

Mean Sequence

$$\begin{aligned} A(s+1) &= A(s) + \lambda_0 + \lambda_1 T(s) - \mu_{RA} R(s) A(s) - \delta_{AM} A(s) \\ &\equiv A(s) + \Delta A(s) \end{aligned} \tag{3.2}$$

$$\begin{aligned} T(s+1) &= T(s) + \tau_C(s) - \delta_T T(s) - \mu_{RT} R(s) T(s) \\ &\equiv T(s) + \Delta T(s) \end{aligned} \tag{3.3}$$

$$\begin{aligned} R(s+1) &= R(s) + \beta\left(\overline{R} - R(s)\right) - \delta_R R(s) - \mu_{RA} R(s) A(s) - \mu_{RT} R(s) T(s) \\ &= R(s) + \Delta R(s) \end{aligned} \tag{3.4}$$

Stochastic Increments

$$\begin{aligned} \Delta A(s) = \lambda_0(s) + \sigma_0(s)\Delta W_0(s) + \lambda_1 T(s) + \sigma_1(s)\Delta W_1(s) - \mu_{RA} R(s) A(s) \\ -\sigma_{RA}(s)\Delta W_{RA}(s) - \delta_{AM} A(s) - \sigma_{AM}(s)\Delta W(s) \end{aligned} \tag{3.5}$$

where

$$\begin{aligned} \sigma_0^2(s) &= \xi_0 \lambda_0(s) \\ \sigma_1^2(s) &= \xi_1 \lambda_1 T(s) \\ \sigma_{RA}^2 &= \xi_{RA} \mu_{RA} R(s) A(s) \\ \sigma_{AM}^2(s) &= \xi_{AM} \delta_{AM} A(s). \end{aligned} \tag{3.6}$$

The terms ΔW_i are mutually independent and Normal/Gaussian with mean 0 and variance 1 (if a different time step, the variance = time step). The constants ξ_0, ξ_1, ξ_{RA}, ξ_{AM}, are introduced so as to allow variability adjustment; putting them all equal to unity simulates a diffusion approximation to a simple birth-death model.

Likewise,

$$\Delta T(s) = \tau_C(s) + \sigma_C(s)\Delta W_C(s) - \delta_T T(s) - \sigma_T(s)\Delta W_T(s) \\ -\mu_{RT} R(s)T(s) - \sigma_{RT}(s)\Delta W_{RT}(s) \tag{3.7}$$

$$\sigma_C^2(s) = \xi_C \tau_C(s)$$

$$\sigma_T^2(s) = \xi_T \delta_T(s) T(s) \tag{3.8}$$

$$\sigma_{RT}^2(s) = \xi_{RT} \mu_{RT} R(s) T(s);$$

finally

$$\Delta R(s) = \beta\left(\overline{R} - R(s)\right) + \sigma_\beta(s)\Delta W_\beta(s) - \delta_R R(s) - \sigma_R(s)\Delta W_R(s) \\ -\mu_{RA} R(s)A(s) - \sigma_{RA}(s)\Delta W_{RA}(s) \\ -\mu_{RT} R(s)T(s) - \sigma_{RT}(s)\Delta W_{RT}(s). \tag{3.9}$$

It should be clear how to write down formulas for σ_β^2 and so forth.

Form the simulation

Realization

by recurrence:

$$A(s+1) = A(s) + \Delta A(s) \tag{3.10}$$

$$T(s+1) = T(s) + \Delta T(s) \tag{3.11}$$

$$R(s+1) = R(s) + \Delta R(s) \tag{3.12}$$

Start from initial conditions. Slight modifications will be necessary near boundaries to retain $R(s)$-values positive and never greater than $\overline{R}$; also $T(s)$ and $A(s)$ positive for all s. Note that there is a Normal/Gaussian Wiener process increment with each incremental component; some are common to two state-variable increments, e.g. ΔW_{RT} is in common with $\Delta T(s)$ and $\Delta R(s)$. The increment components that are not common to others can be combined so as to make necessary generation of just one (independent) increment component.

Mathematical Theory

Features of the escape from the neighborhood of either of two possible local stability points can be treated mathematically; this topic is called the *exit problem,* and is related to the *theory of large deviations.* Prominent contributors are Schuss (1980), Varadhan (1984), Aldous (1989), Simonian (1995), Freidlin and Wentzell (1984). An accessible textbook is Bucklew (1990). Attempts to mathematically calculate features of the process of jumping between stable points are not made in this paper; the qualitative features of the process are well-illustrated by simulation results.

Examples

Figure 3 through Figure 8 illustrate hypothetical time developments of adduct populations and corresponding amounts of enzyme. The initial values of A, R, and T are set equal to the largest root, R_U, of the cubic equation equivalent to (3.1) and the corresponding values of A and T; the $\xi_C = 16$ and the other $\xi_i = 1$. Two replications are displayed in Figures 3 – 5; both depend on the same parameters, but flare-ups of adducts appear at quite different times; these high-adduct periods correspond to jumps from R_U to R_L (and in the present case rather quickly back), which are triggered by high fluctuations in internal toxin $T(t)$ caused initially by random fluctuations in $\tau(t)$, the amount of toxic chemical entering the cell. Figure 6 displays results for one replication. Figures 7 – 9 display the time series of the amount of enzyme, the number of adducts, and the amount of toxin along with histograms of the values. The histogram of the amount of enzyme has the most pronounced bimodal appearance. The lesser apparent bimodality in the histograms of number of adducts and the amount of toxin may reflect the fact that the derivatives of these two quantities are functions of the amount of enzyme and so the number of adducts and the amount of toxin

tend to be more related to the area under the enzyme time series and are thus smoothed. In these figures, all based on hypothetical parametric values, bistability is plainly visible. A burst of adducts can be expected to precede and trigger off other events upon successive replication after fixation of single or multiple mutations. Another possibility, also not currently modeled, is the possibility of actual cell death through necrosis or apoptosis when the intracellular toxin is relatively high and adducts are present.

4. Discussion

DNA abnormalities, e.g. adducts related to chemical exposure, are linked to mutation and the process of carcinogenesis. Hence their existence and relative prevalence within a tissue or cell may be useful as a risk analysis tool. However, the number of DNA adducts within any given cell of an organism on a temporal scale after acute or chronic exposures may be highly variable as a function of many interrelated biological processes.

In the present non-linear dynamic model the possible effect of initial conditions is dramatically illustrated: even a sudden brief shift of intra-cellular toxic chemical concentration can initiate a qualitative shift in cell condition, both inducing adduct formation and hobbling the cell's repair mechanism by binding the repair enzyme. The biological significance of the model is that such shifts, occurring within a context of replication across a number of cells can lead to adduct fixation as mutation and preconditions for transformation depending on the site, penetrance and expressivity of the event. The effect may be selective for individuals in the sense that some may have more resistance to assault owing to greater repair capability: larger enzyme production attributable to relatively larger values of β and $\overline{R}$ in (2.3), perhaps leading to a greater-than-average repair enzyme concentration. Alternatively, there could exist a greater selectivity

in binding of the repair enzyme to DNA adducts rather than toxin, i.e. $\mu_{RA} > \mu_{RT}$ in (2.2) and (2.3) in some individual or tissues, thus leading to greater resistance to toxin. On the other hand, if propensity to form adducts is characteristic of at least some cells, i.e. reflected in relatively large parameters λ_0 and λ_1, and perhaps also in outsized fixation rate δ_{AM}, see (2.1), then there can be inter-individual variations that could quantitatively describe an inherited predisposition to cancer as discussed by Sommerfeld, Meeker, Posadas, and Coffey (1995). This characteristic would be independent of the many preexisting mutations in genes known to be involved in the appearance of cancer in certain individuals.

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APPENDIX
The Cubic Equation for Enzyme Fixed Points

The cubic equation that describes the fixed points of (2.1) – (2.3), specifically the solutions of (3.1), is as follows.

$$
\begin{aligned}
&(\beta+\delta_R)\mu_{RA}\mu_{RT}R^3 \\
&+\left[-\beta\bar{R}\mu_{RA}\mu_{RT}+(\beta+\delta_R)(\mu_{RA}\delta_T+\mu_{RT}\delta_{AM})+\lambda_0\mu_{RA}\mu_{RT}+\tau_C\mu_{RT}\mu_{RA}\right]R^2 \\
&+\left[-\beta\bar{R}(\mu_{RA}\delta_T+\mu_{RT}\delta_{AM})+(\beta+\delta_R)\delta_{AM}\delta_T+\lambda_0\mu_{RA}\delta_T+\lambda_1\tau_C\mu_{RA}+\tau_C\mu_{RT}\delta_{AM}\right]R \\
&-\beta\bar{R}\,\delta_{AM}\delta_T=0;
\end{aligned}
\tag{A.1}
$$

division by $(\beta+\delta_R)\mu_{RA}\mu_{RT}$ puts this into the form in C.R.C. Standard Mathematical Tables or Press *et al.* (1992).

$$x^3+ax^2+bx+c=0 \tag{A.2}$$

where

$$
\begin{aligned}
a&=\frac{\left[-\beta\bar{R}\mu_{RA}\mu_{RT}+(\beta+\delta_R)(\mu_{RA}\delta_T+\mu_{RT}\delta_{AM})+(\lambda_0+\tau_C)\mu_{RA}\mu_{RT}\right]}{(\beta+\delta_R)\mu_{RA}\mu_{RT}} \\
b&=\frac{\left[-\beta\bar{R}(\mu_{RA}\delta_T+\mu_{RT}\delta_{AM})+(\beta+\delta_R)\delta_{AM}\delta_T+\lambda_0\mu_{RA}\delta_T+\lambda_1\tau_C\mu_{RA}+\tau_C\mu_{RT}\delta_{AM}\right]}{(\beta+\delta_R)\mu_{RA}\mu_{RT}} \\
c&=\frac{-\beta\bar{R}\delta_{AM}\delta_T}{(\beta+\delta_R)\mu_{RA}\mu_{RT}}.
\end{aligned}
\tag{A.3}
$$

Next, put

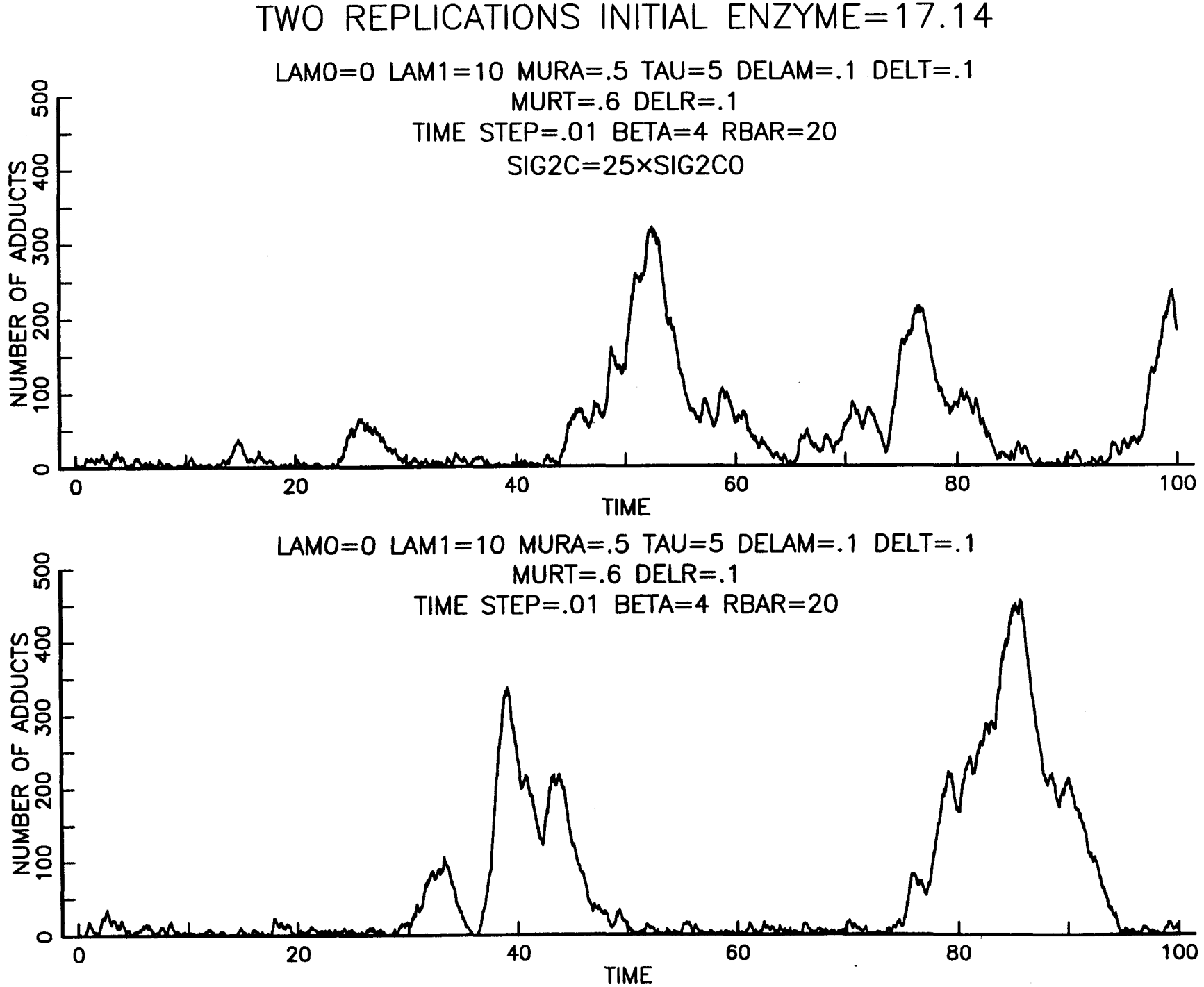
$$Q=\frac{a^2-3b}{9},\quad S=\frac{2a^3-9ab+27c}{54}. \tag{A.4}$$

If $S^2 < Q^3$ there are three real roots; if $S^2 > Q^3$ there is one real root (and two imaginaries); if $S^2 = Q^3$ there will be equal roots.

No attempt has been made to simplify or interpret the formidable algebraic expressions that are obtained from the above formal manipulations. Note, however, that if there is no toxin input, i.e. $\tau_C(t) \equiv 0$, then $T(t) = 0$ and the cubic A reduces to the quadratic

$$(\beta + \delta_R)\mu_{RA}R^2 + \left[-\beta\overline{R}\mu_{RA} + (\beta + \delta_R)\delta_{AM} + \lambda_0\mu_{RA}\right]R - \beta\overline{R}\delta_{AM} = 0 \qquad \text{(A.5)}$$

It is apparent from the explicit solution that there will always be one positive fixed point, which will be the largest solution of (A.5). This will be a stable point. This conclusion follows directly from a graphical argument like that used before.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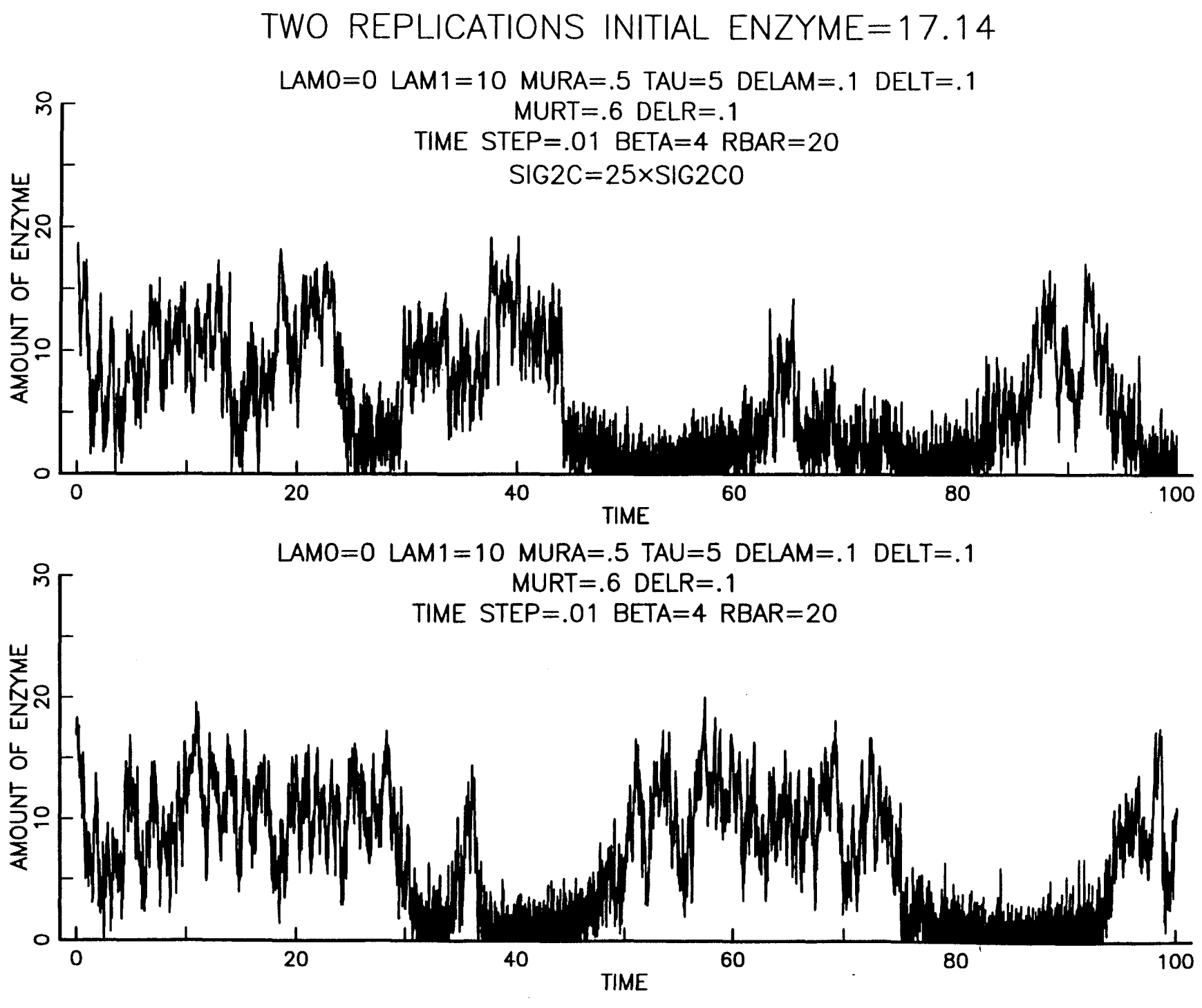
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
SIG2C=25×SIG2C0
NUMBER OF ADDUCTS
0
100
200
300
400
500
0
20
40
60
80
100
TIME
LAM0=0 LAM1=10 MURA=.5 TAU=5 DELAM=.1 DELT=.1
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
NUMBER OF ADDUCTS
0
100
200
300
400
500
0
20
40
60
80
100
TIME

Figure 3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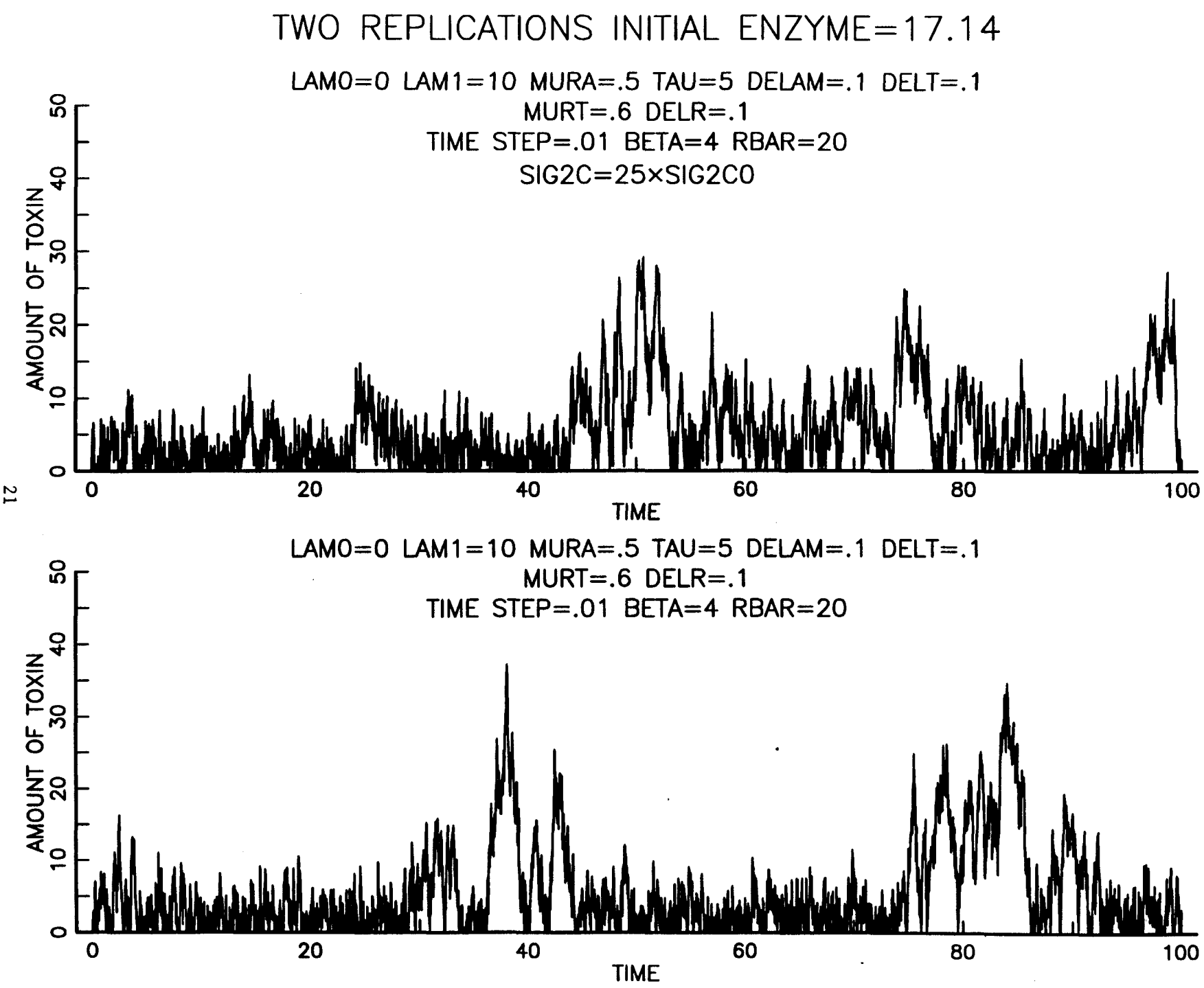
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
SIG2C=25×SIG2C0
AMOUNT OF ENZYME
0
10
20
30
0
20
40
60
80
100
TIME
LAM0=0 LAM1=10 MURA=.5 TAU=5 DELAM=.1 DELT=.1
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
AMOUNT OF ENZYME
0
10
20
30
0
20
40
60
80
100
TIME

Figure 4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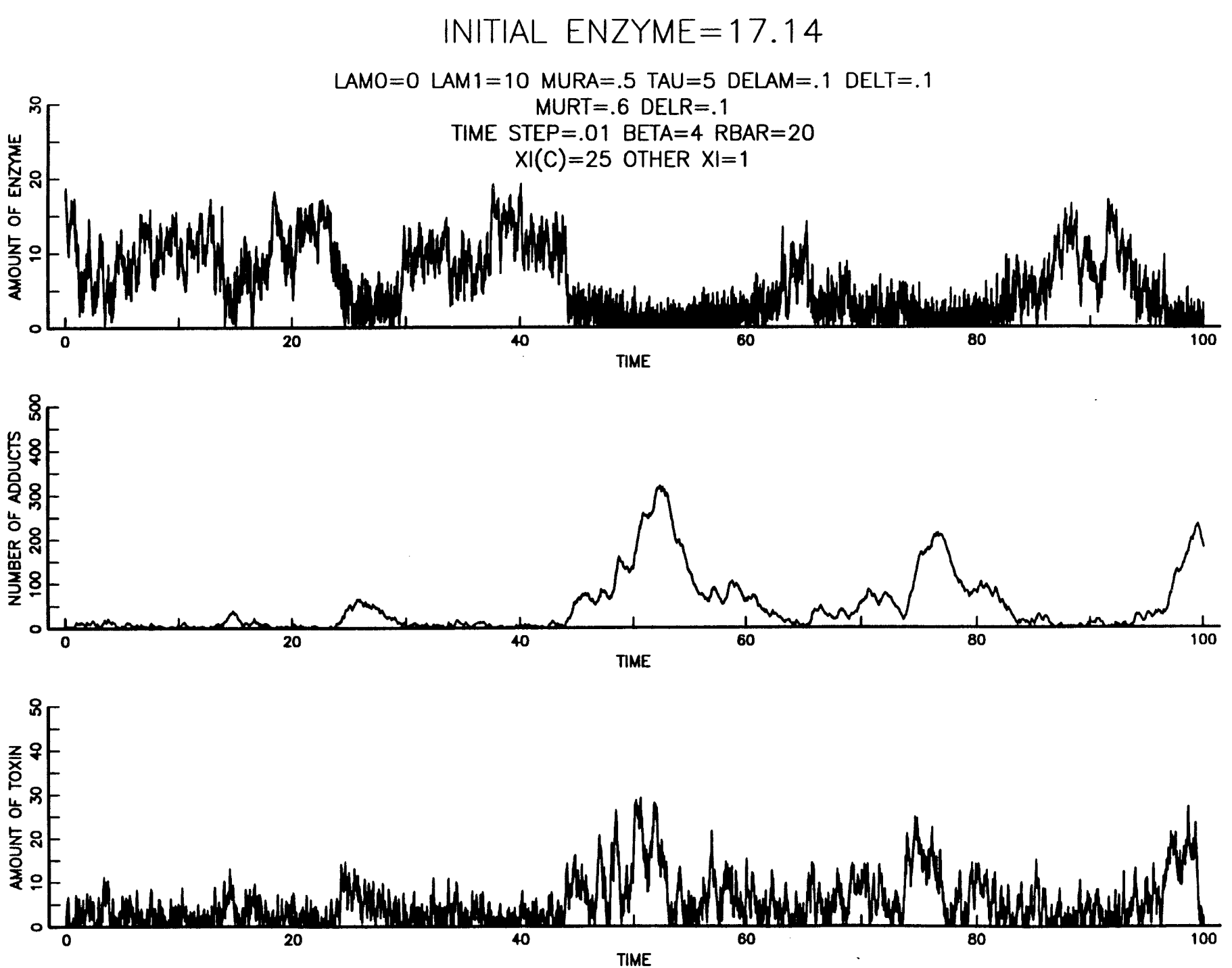
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
SIG2C=25×SIG2C0
AMOUNT OF TOXIN
0
10
20
30
40
50
0
20
40
60
80
100
TIME
LAM0=0 LAM1=10 MURA=.5 TAU=5 DELAM=.1 DELT=.1
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
AMOUNT OF TOXIN
0
10
20
30
40
50
0
20
40
60
80
100
TIME

Figure 5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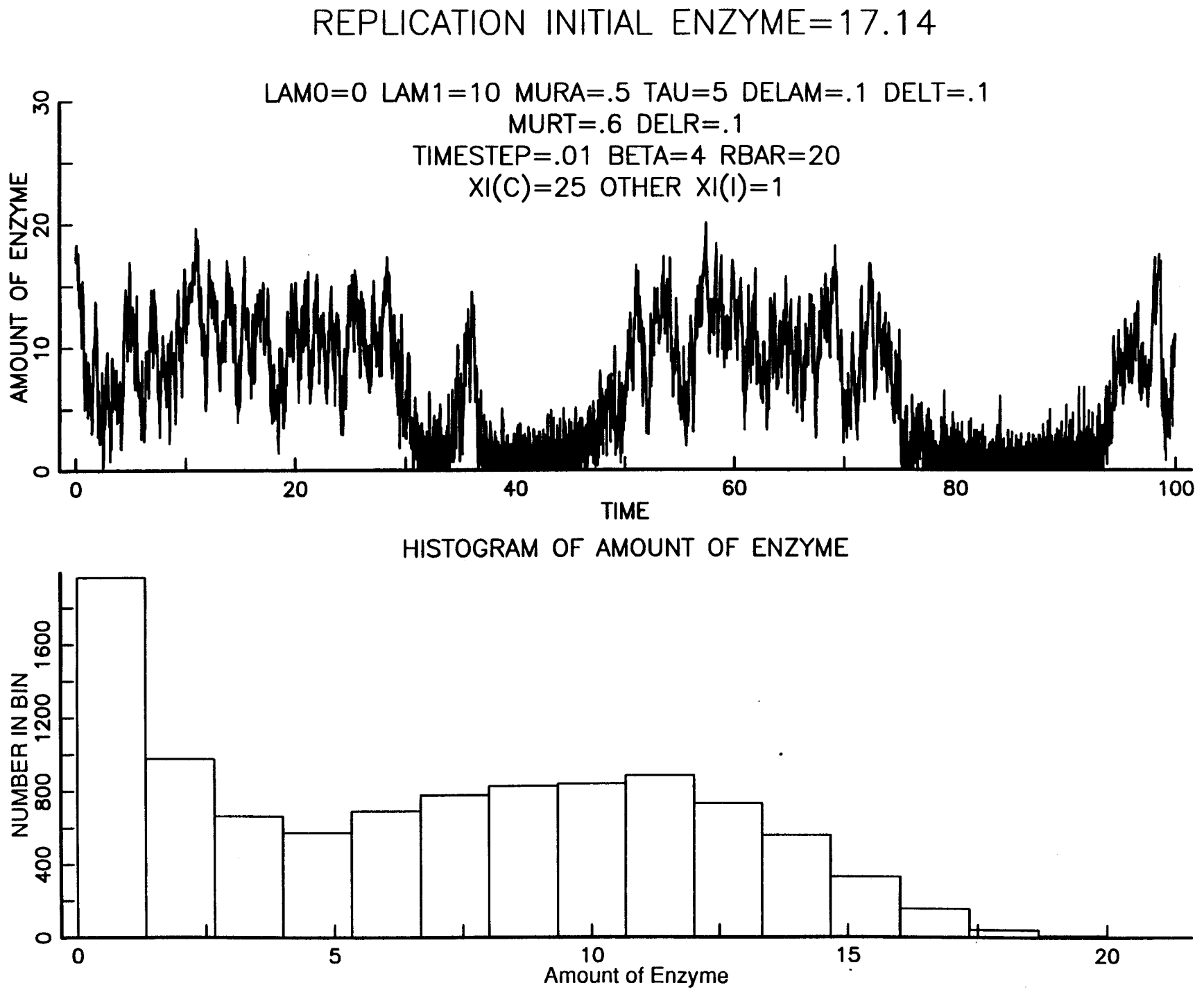
MURT=.6 DELR=.1
TIME STEP=.01 BETA=4 RBAR=20
XI(C)=25 OTHER XI=1
AMOUNT OF ENZYME
0
10
20
30
0
20
40
60
80
100
TIME
NUMBER OF ADDUCTS
0
100
200
300
400
500
0
20
40
60
80
100
TIME
AMOUNT OF TOXIN
0
10
20
30
40
50
0
20
40
60
80
100
TIME

Figure 6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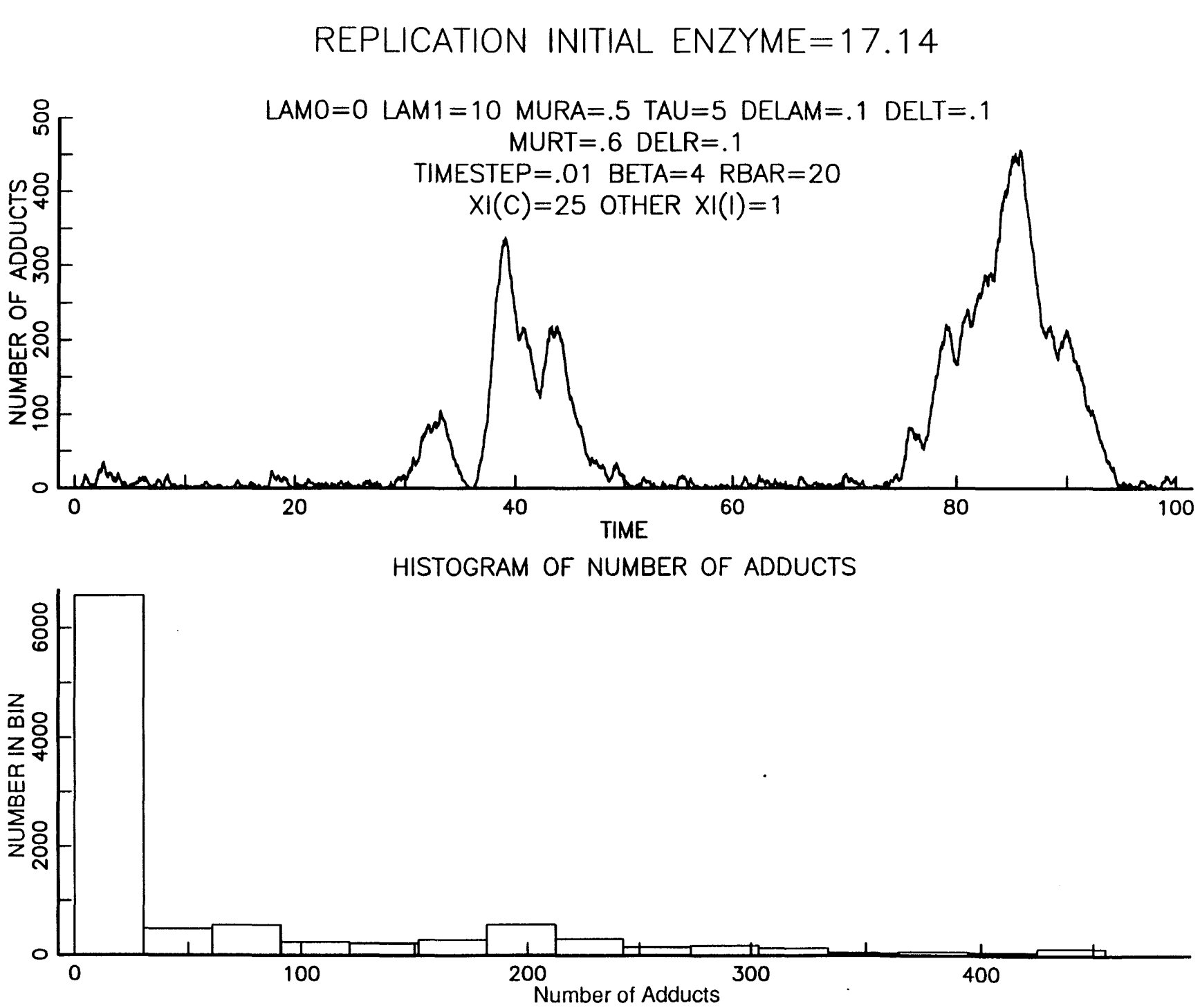
LAM0=0 LAM1=10 MURA=.5 TAU=5 DELAM=.1 DELT=.1
MURT=.6 DELR=.1
TIMESTEP=.01 BETA=4 RBAR=20
XI(C)=25 OTHER XI(I)=1
AMOUNT OF ENZYME
0
10
20
30
0
20
40
60
80
100
TIME
HISTOGRAM OF AMOUNT OF ENZYME
NUMBER IN BIN
0
400
800
1200
1600
0
5
10
15
20
Amount of Enzyme

Figure 7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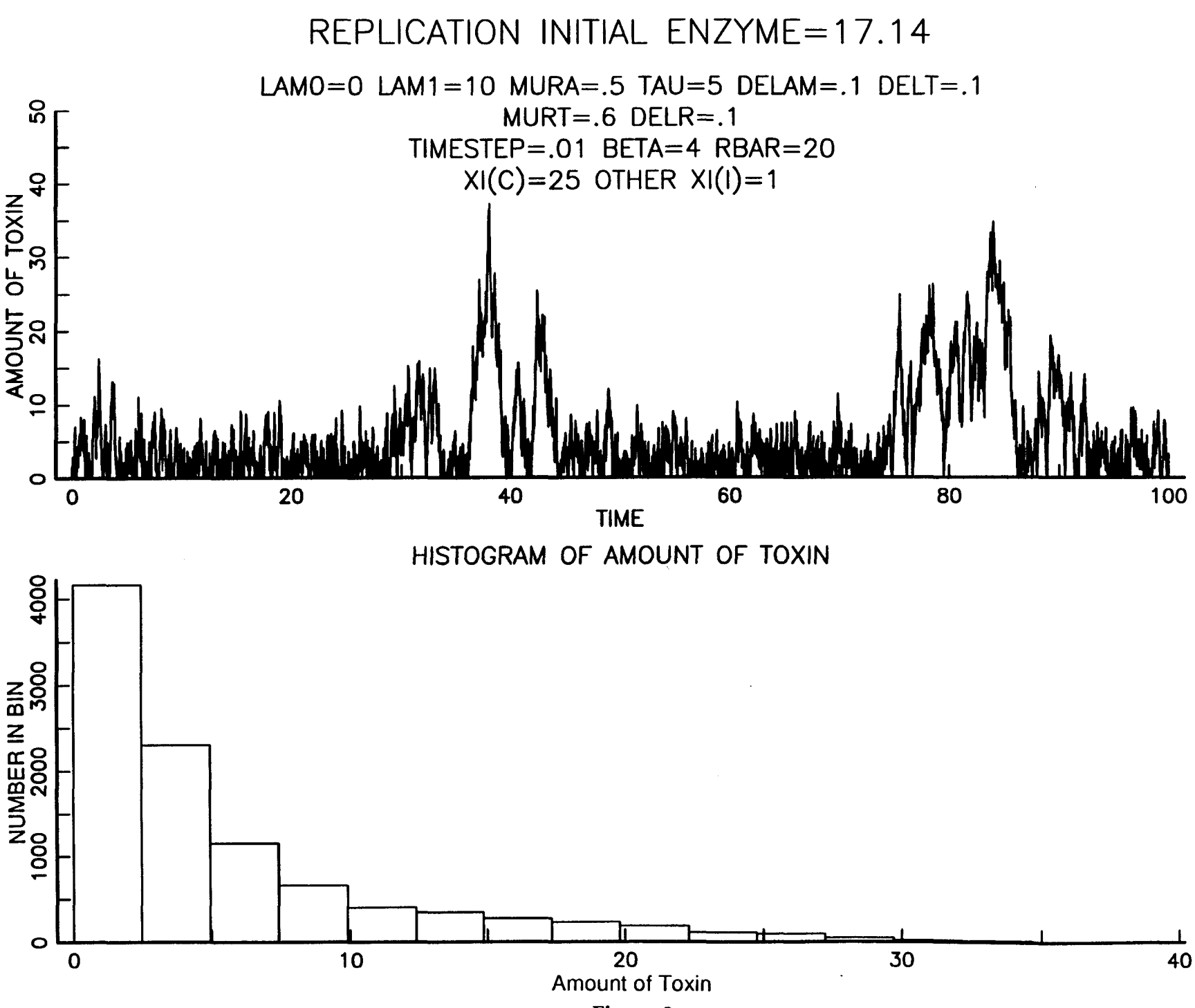
LAM0=0 LAM1=10 MURA=.5 TAU=5 DELAM=.1 DELT=.1
MURT=.6 DELR=.1
TIMESTEP=.01 BETA=4 RBAR=20
XI(C)=25 OTHER XI(I)=1
NUMBER OF ADDUCTS
0
100
200
300
400
500
0
20
40
60
80
100
TIME
HISTOGRAM OF NUMBER OF ADDUCTS
NUMBER IN BIN
0
2000
4000
6000
0
100
200
300
400
Number of Adducts

Figure 8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LAM0=0 LAM1=10 MURA=.5 TAU=5 DELAM=.1 DELT=.1
MURT=.6 DELR=.1
TIMESTEP=.01 BETA=4 RBAR=20
XI(C)=25 OTHER XI(I)=1
AMOUNT OF TOXIN
0
10
20
30
40
50
0
20
40
60
80
100
TIME
HISTOGRAM OF AMOUNT OF TOXIN
NUMBER IN BIN
0
1000
2000
3000
4000
0
10
20
30
40
Amount of Toxin

Figure 9

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